

The Value of New Chemotherapeutic Agents for Metastatic Colorectal Cancer

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Background: New chemotherapeutic agents for patients diagnosed with metastatic colorectal cancer have been singled out as examples of high-cost/low-value medical care. We measure trends in life expectancy and lifetime medical costs in this patient population between January 1, 1995, and December 31, 2005.

Methods: Using the Surveillance, Epidemiology, and End Results–Medicare database, we constructed a sample of 4665 patients aged 66 and older diagnosed with metastatic colorectal cancer between January 1, 1995, and December 31, 2005, who received chemotherapeutic agents. We estimated life expectancy and lifetime medical costs based on observed short-term survival rates and costs.

Results: Life expectancy increased by 6.8 months and lifetime costs by \$37 100 (2006 dollars). The implied cost

per life-year gained is \$66 200 (95% confidence interval, \$48 100–\$84 200). After discounting life-years and costs and adjusting for patients' health utility and out-of-pocket payments, the cost per quality-adjusted life-year gained is \$99 100 (95% confidence interval, \$72 300–\$125 900).

Conclusions: New chemotherapeutic agents are associated with improvements in survival time but also with substantial costs. The cost-effectiveness ratio for these drugs as a group is below commonly cited estimates of the willingness-to-pay for a life-year. However, open-ended coverage policies for new chemotherapeutic agents may prove difficult to sustain as costs continue to rise.

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BETWEEN JUNE 14, 1996, AND February 26, 2004, the US Food and Drug Administration approved 6 chemotherapeutic agents for treatment of metastatic colorectal cancer. These drugs, bevacizumab (Avastin; Genentech Inc, South San Francisco, California) and cetuximab (Erbix; Bristol-Myers Squibb, Princeton, New Jersey) in particular, have been singled out as examples of high-cost/low-value medical care. In randomized controlled trials, bevacizumab extended median survival time by only 3 to 5 months,¹⁻⁴ yet the cost can exceed \$8000 monthly.

In this study, we compare trends in life expectancy and lifetime medical costs for Medicare patients diagnosed with metastatic colorectal cancer and treated with chemotherapeutic agents between January 1, 1995, and December 31, 2005. Assuming that, in the absence of new chemotherapeutic agents, costs and survival in this population would have remained largely unchanged, an assumption supported by the absence of trends in survival and costs for patients not treated with chemotherapeutic agents, we can measure the cost-effectiveness of these drugs

as a group by comparing the change in costs to the change in survival time.

Previously, Cutler and colleagues^{5,6} used this approach to estimate the value of new treatments for patients who experienced a heart attack. They found that while spending on medical care for these patients increased rapidly in the early 1990s, the gains in survival time were large relative to the increase in costs. More recently, Cutler and Meara,⁷ Eggleston et al,⁸ and Woodward et al⁹ demonstrated that new medical technologies for low-birth-weight infants and patients with diabetes are very cost-effective,⁷ while those for patients with lung cancer are less so.^{8,9}

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METHODS

DATA

The sample was drawn from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, which consists of SEER tumor registry records linked with Medicare claims. We used records from the SEER registries that have reported incident cases since January 1, 1992, or earlier. The data include Medicare claims between January 1, 1995, and December 31, 2006, and vital status between January 1, 1995, through December 31, 2007.

SAMPLE

The sample consists of 12 473 patients aged 66 and older diagnosed with stage IV colorectal cancer between January 1, 1995, and December 31, 2005. We included patients enrolled in Parts A and B of fee-for-service Medicare 1 year prior to diagnosis and for at least 2 years following diagnosis or until death.

Rather than comparing trends across calendar years, we divided the sample into 5 groups based on the date of diagnosis. We used the US Food and Drug Administration approval date of new chemotherapeutic agents to demarcate the groups: irinotecan hydrochloride (Camptosar; Pfizer Inc, New York, New York), June 14, 1996; capecitabine (Xeloda; Roche Laboratories Inc, Basel, Switzerland), April 30, 1998; oxaliplatin (Eloxatin; Sanofi-Aventis LLC, Bridgewater, New Jersey), August 9, 2002; and bevacizumab (Avastin) and cetuximab (Erbix), February 12 and 26, 2004, respectively. Group 1 includes patients diagnosed between January 1, 1995, and May 31, 1996, group 2 includes patients diagnosed between June 30, 1996, and March 30, 1998, and so on.

We further split the sample into 2 groups: patients treated initially with chemotherapeutic agents and patients who did not receive chemotherapeutic agents as a primary treatment. We counted a patient as receiving chemotherapeutic agents if he or she had at least 1 claim with a chemotherapy administration code (Healthcare Common Procedures Classification System¹⁰ codes 964XX, 965XX, Q0083-Q0085, G0355, G0359, and *International Classification of Diseases, Ninth Revision*¹¹ diagnosis codes V58.1, V66.2, V67.2 and procedure code 99.25) or any claim for one of the drugs listed in the previous paragraph or fluorouracil or leucovorin calcium (folinic acid) within 6 months of diagnosis. Warren and coauthors,¹² in the Patterns of Care Study, report that Medicare claims correctly identified 90% of patients with colorectal cancer receiving chemotherapeutic agents.

We measured the proportion of patients receiving irinotecan, oxaliplatin, and bevacizumab within 6 months of diagnosis. We were unable to measure receipt of capecitabine (which is billed using National Drug Classification codes), although the costs of the drug are included in our analysis. Of patients diagnosed in 2005, only 2.7% received cetuximab within 6 months of diagnosis.

We also measured receipt of hepatic resection. We counted the number of patients with an inpatient claim listing diagnosis-related groups 191 or 192 (pancreas, liver, and shunt procedures with and without comorbidity/complications) in the year following diagnosis. We constructed a comorbidity index using the *International Classification of Diseases, Ninth Edition*, codes on physician office, outpatient, and inpatient claims.¹³

LIFE EXPECTANCY

We calculated empirical survival curves through 5 years after diagnosis for the first 3 groups. For patients in the second-to-last group, we calculated empirical survival curves through 4 years after diagnosis. The fourth year is the last full year for which we can observe survival for all patients in this group. To project the survival curve beyond 4 years, we assumed that mortality rates in year 5 would be the same as those for patients in the third group.

We used a similar approach to calculate survival curves for the last group, with survival curves based on empirical survival rates for years 1 through 3 and historical survival rates for years 4 and 5. For all groups, we projected mortality rates in year 6 and beyond by assuming that mortality rates in year 5 increase by 9% annually, based on US life tables.¹⁴ We calculated life expectancy by summing the area under the survival curve. To cal-

culate quality-adjusted life-years (QALYs), we assumed that patients' health utility rate after diagnosis is 0.8.¹⁵

LIFETIME COSTS

We calculated lifetime medical costs separately for each group. Costs represent Medicare reimbursements and were inflated to 2006 dollars using Medicare's Medical Economic Index¹⁶ for physician payments and the Prospective Payment System Hospital Input Price Index¹⁷ for all other reimbursements. To the extent that these price indices overstate the true rate of inflation, our estimates of increases in real costs and cost-effectiveness will be biased upward.

Lifetime medical costs are a weighted sum of costs incurred by patients who died within 2 years and costs incurred by patients alive at the 2-year mark. We chose 2 years as the cutoff because 2 years is the maximum period for which we can observe costs for all patients in the last group.

For patients who died within 2 years, we calculated average costs from diagnosis to death. For patients who survived for 2 years or longer, we estimated lifetime costs using a variation on the phase-of-care approach.¹⁸ We calculated (1) *initial costs*: costs in the 2 years following diagnosis, (2) *ongoing costs*: costs incurred between 2 years after diagnosis and 1 year before death, and (3) *end-of-life costs*: costs incurred in the year prior to death. Separately, we used the predicted survival curves to estimate life expectancy at 2 years, conditional on surviving to that point. Lifetime medical costs are initial costs plus end-of-life costs plus monthly ongoing costs multiplied by the number of months spent in the ongoing-care phase (survival time [in months] beyond 2 years, minus 12). We tested the accuracy of our cost estimates by comparing estimated lifetime costs with actual costs incurred from diagnosis through December 31, 2006 (the last date for which we have Medicare claims) for the first 2 groups. We calculated out-of-pocket costs by applying Medicare's statutory cost-sharing formulas to Medicare reimbursements.

An example is useful for illustrating this approach. Suppose 80% of patients die within 2 years and their average costs are \$20. Suppose further that for patients who survive beyond 2 years, initial costs are \$12, ongoing costs are \$1 monthly, and end-of-life costs are \$10. If life expectancy at 2 years after diagnosis is 20 months, then we would estimate that lifetime costs are:

$$\$22 = (0.8 \times \$20) + 0.2 \times (\$12 + [\$1 \times 8] + \$10).$$

The middle term (ie, 8) is the number of months spent in the "ongoing" care phase. It is multiplied by average monthly ongoing costs.

STATISTICAL ANALYSIS

We standardized estimates for comorbidity by calculating life expectancy and costs separately for beneficiaries with 0, 1, or 2 or more comorbidities and taking the weighted sum, where the weights equal the proportion of beneficiaries in each comorbidity group, across the entire sample. We used the log-rank test to test the significance of trends in median survival. We used regression analysis to test the significance of trends in other variables of interest. The regression models included an intercept term and a time trend variable equal to the year of diagnosis minus 1995. We used a generalized linear model with a log link and gamma variance structure¹⁹ to assess the statistical significance of differences in short-term costs between groups. We used least squares regression for age; logistic regression for sex; and Poisson regression for the number of comorbidities. We used nonparametric bootstrapping with bias-corrected standard errors and 1000 replications to estimate

Table 1. Trends in Patient Demographics, Median Survival Time, and Short-Term Costs

	Time Period					P Value
	Jan 1, 1995, to May 31, 1996	Jun 1, 1996, to Mar 31, 1998	Apr 1, 1998, to Jul 31, 2002	Aug 1, 2002, to Jan 31, 2004	Feb 1, 2004, to Dec 31, 2005	
Patients treated with chemotherapeutic agents (n=4665)						
Patients, No. (%)	667 (14.3)	829 (17.8)	1746 (37.4)	584 (12.5)	839 (18.0)	
Mean age, y	74.7	74.8	75.0	75.0	74.7	.46
Male sex, No. (%)	354/667 (53)	440/829 (53)	912/1746 (52)	284/584 (49)	429/839 (51)	.45
Comorbidities						
0	0.63	0.50	0.52	0.48	0.46] <.001
1	0.22	0.28	0.26	0.28	0.28	
≥2	0.15	0.23	0.22	0.24	0.26	
Median survival time, mo	11.6	12.6	13.7	14.7	16.1	<.001
Costs (in thousands), \$						
1 Year before diagnosis	2.2	4.7	4.4	4.6	5.5	<.001
2 Years after diagnosis	56.6	59.9	61.8	78.0	81.0	<.001
Patients not treated with chemotherapeutic agents (n=7808)						
Patients, No. (%)	1098 (14.1)	1431 (18.3)	2938 (37.6)	1030 (13.2)	1311 (16.8)	
Mean age, y	79.2	79.8	80.0	79.8	80.6	.002
Male sex, No. (%)	472/1098 (43)	653/1431 (46)	1341/2938 (46)	481/1030 (47)	592/1311 (45)	.45
Comorbidities						
0	0.71	0.58	0.56	0.59	0.53] <.001
1	0.21	0.27	0.28	0.25	0.25	
≥2	0.08	0.15	0.16	0.16	0.22	
Median survival time, mo	2.9	2.8	2.6	2.9	2.5	.54
Costs (in thousands), \$						
1 Year before diagnosis	4.6	8.3	6.4	6.5	8.1	.01
2 Years after diagnosis	38.4	38.1	38.4	40.4	39.6	.13

confidence intervals for life expectancy and lifetime medical cost and cost-effectiveness acceptability curves for incremental cost-effectiveness ratios.

RESULTS

The final sample consisted of 12 473 patients, of whom 4665 (37.4%) received chemotherapeutic agents within 6 months of diagnosis. **Table 1** displays demographic characteristics, median survival time, and costs before diagnosis and after diagnosis. The proportion of patients receiving chemotherapeutic agents was constant during the study period. Among patients receiving chemotherapeutic agents, median survival time increased by 4.5 months, and costs in the 2-year window following diagnosis increased by \$17 800.

Figure 1 displays the proportion of patients receiving chemotherapeutic agents who were treated with irinotecan, oxaliplatin, and bevacizumab within 6 months of diagnosis. This proportion is calculated based on incident rather than prevalent cases in each month, and so the proportion of patients receiving each drug begins to increase before the drug's US Food and Drug Administration approval date. The figure shows that the use of irinotecan increased slowly and then declined, while that of oxaliplatin and bevacizumab declined rapidly.

Figure 2 displays survival curves for patients who received chemotherapeutic agents within 6 months of diagnosis. The lines represent the portion of the survival curves based on empirical survival rates. Survival rates steadily increased during the study period. For example, 19.1% of pa-

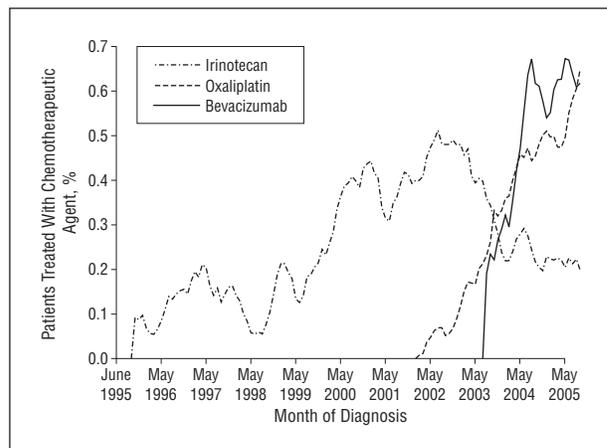


Figure 1. Diffusion of new chemotherapeutic agents among patients treated with chemotherapy, by month of diagnosis (as given in 5-month moving average increments).

tients in the final period were alive at 3 years after diagnosis compared with only 11.7% in the first period.

Estimates of life expectancy and lifetime medical costs are displayed in **Table 2**. There were only small differences between estimated lifetime and actual long-run costs for patients receiving chemotherapeutic agents diagnosed in the first period (estimated: \$63 200; actual through 9 years after diagnosis: \$65 800) and second period (estimated: \$66 600; actual through 7 years after diagnosis: \$68 600).

Life expectancy and lifetime medical costs among patients not receiving chemotherapeutic agents were basically unchanged during the study period. Among pa-

tients receiving chemotherapeutic agents, life expectancy increased by 6.8 months and lifetime costs by \$37 100. The implied cost-effectiveness ratio is \$66 200 (95% confidence interval [CI], \$48 100-\$84 200) per life-year gained.

When life-years and costs are discounted by 3.0%, patients' health utility after diagnosis is assumed to be 0.80, and we include patients' estimated out-of-pocket costs for Medicare-covered services, the incremental cost per QALY gained is \$99 100 (95% CI, \$72 300-\$125 900). The proportion of patients treated with chemotherapeutic agents who underwent hepatic resection varied from 2.5% to 6.0%. Exclusion of patients who underwent hepatic resection had no effect on the incremental cost-effectiveness ratio: \$100 763 (95% CI, \$73 525-\$128 001). If patients' health utility after diagnosis is only 0.6 instead of 0.8, the incremental cost per QALY gained is \$132 669 (95% CI, \$95 335-\$170 003). If health utility is 1.0, the cost per QALY gained is \$78 955 (\$58 542-\$99 368).

We also calculated incremental cost-effectiveness ratios based on period-to-period changes in life expectancy and costs. The ratios and the new drug in the second of the 2 periods are as follows: \$30 700 (irinotecan), \$37 800 (capecitabine), \$111 200 (oxaliplatin), and \$40 500 (bevacizumab). Confidence intervals for these incremental cost-effectiveness ratios were not well defined, so we present uncertainty in the estimates using cost-effectiveness ac-

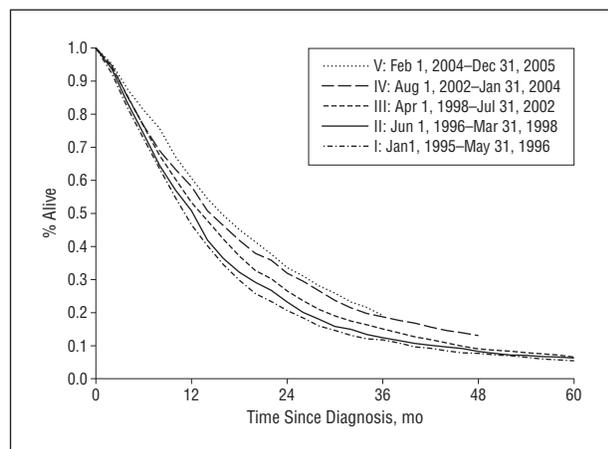


Figure 2. Survival curves by era of diagnosis.

ceptability curves in **Figure 3**. The height of the curve shows the proportion of bootstrap estimates in which the incremental cost-effectiveness ratio is below the threshold on the x-axis.

COMMENT

Between January 1, 1995, and December 31, 2005, there were sizable increases in life expectancy and lifetime medical costs among elderly (ie, age 66 or older) Medicare beneficiaries diagnosed with metastatic colorectal cancer and treated with chemotherapeutic agents. On balance, the cost per QALY gained was about \$100 000.

Previous studies have used traditional decision-modeling approaches for estimating cost-effectiveness based on clinical trials. These have reported cost-effectiveness ratios in the same range or larger than ours: \$102 000 for a regimen using irinotecan as first-line therapy and oxaliplatin as second-line therapy vs fluorouracil and leucovorin calcium,²⁰ \$171 000 for bevacizumab vs irinotecan followed by oxaliplatin,²⁰ \$65 000 for oxaliplatin vs

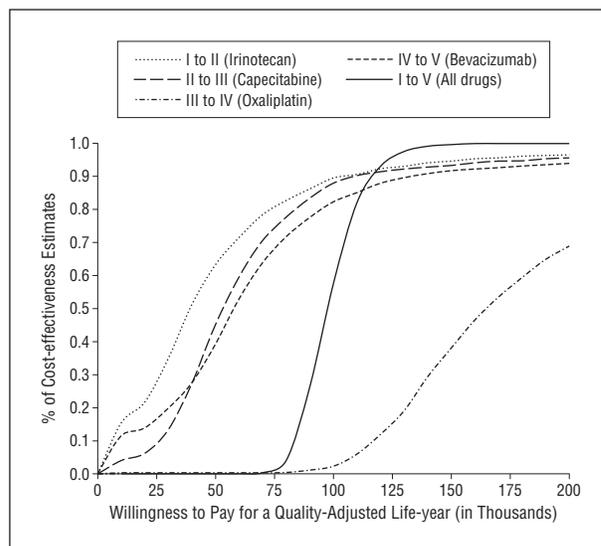


Figure 3. Cost-effectiveness acceptability curves. Each line describes the proportion of bootstrap estimates in which the incremental cost-effectiveness ratio, defined as the ratio of change in costs to change in survival time between periods, falls below willingness-to-pay thresholds on the x-axis.

Table 2. Trends in Life Expectancy and Lifetime Medical Costs

	Months/Costs in Thousands, \$ (95% Confidence Interval)					Change
	Time Period					
	Jan 1, 1995, to May 31, 1996	Jun 1, 1996, to Mar 31, 1998	Apr 1, 1998, to Jul 31, 2002	Aug 1, 2002, to Jan 31, 2004	Feb 1, 2004, to Dec 31, 2005	
Patients treated with chemotherapeutic agents						
Life expectancy	16.5 (14.7 to 18.4)	17.8 (15.9 to 19.8)	19.4 (17.7 to 21.1)	22.0 (19.4 to 24.6)	23.4 (20.9 to 25.8)	6.8 (4.7 to 9.0)
Lifetime costs	63.2 (58.1 to 68.2)	66.6 (61.4 to 71.7)	71.4 (66.4 to 76.5)	95.7 (86.5 to 104.8)	100.3 (91.6 to 108.9)	37.1 (30.1 to 44.0)
Patients not treated with chemotherapeutic agents						
Life expectancy	7.6 (6.8 to 8.5)	7.9 (7.0 to 8.7)	7.8 (7.1 to 8.5)	8.1 (7.1 to 9.0)	7.5 (6.7 to 8.3)	-0.01 (-0.10 to 0.07)
Lifetime costs	40.5 (37.4 to 43.7)	40.5 (37.4 to 43.6)	41.0 (38.1 to 43.9)	43.7 (39.7 to 47.6)	42.3 (38.9 to 45.7)	1.8 (-1.1 to 4.7)

irinotecan,²¹ and £88 436 (\$142 850) for bevacizumab with or without fluorouracil and leucovorin calcium.²²

The study design assumes that the population of elderly Medicare patients diagnosed with metastatic colorectal cancer and treated with chemotherapeutic agents has been relatively stable over time in terms of health status and prognosis at diagnosis. This assumption would be violated if, because of increased use of screening or imaging, patients in the later years of the study period were diagnosed earlier in the course of their disease or with less aggressive tumors. Screening rates increased in the late 1990s and early 2000s, but the magnitude of the increase was small, with increases in the use of colonoscopy partially offset by declines in the use of other screening modalities.²³

The validity of the assumption that survival and costs are comparable between patients diagnosed early and later in the study period is supported by 2 observations. First, the proportion of patients treated with chemotherapeutic agents was stable. Second, there was no change in life expectancy and lifetime costs among patients not treated with chemotherapeutic agents. These observations suggest that our estimates are not subject to lead-time or length-time bias.

We estimated that median survival time among patients diagnosed in the last period was 16.1 months. By contrast, recent clinical trials have reported median survival times exceeding 20 months for regimens containing bevacizumab.²⁴ One reason for the discrepancy is that not all the patients diagnosed in the last period treated with chemotherapeutic agents received bevacizumab. Also, it is not uncommon to see a lower magnitude of benefit when clinical trial regimens are applied in real-world settings to a broader patient population.

The finding that lifetime costs among patients treated with chemotherapeutic agents increased by only \$37 000 seems to contradict the much larger figures typically quoted in the media and journal commentaries for the cost of new chemotherapeutic agents.²⁵ There are a few reasons for the discrepancy. First, not all patients treated with chemotherapeutic agents receive the newest agents. Second, commonly cited figures are based on manufacturers' average wholesale prices. Following passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Medicare reimbursed providers based on each manufacturer's average sale price. Third, commonly cited figures represent costs for 6 or 12 months of therapy. Yet, many patients die or discontinue therapy within 1 year of diagnosis.

Our estimates of the change in survival and costs are lower than they would be if all patients treated with chemotherapeutic agents received the newest agents. However, inclusion of these patients in the chemotherapeutic agents group does not influence the ratio of the change in costs to the change in survival time. Thus, we are able to identify the cost-effectiveness of new chemotherapeutic agents as a group even though not all patients treated with chemotherapeutic agents receive them.

Our sample included only elderly patients. While these patients can benefit from aggressive chemotherapeutic agents, the magnitude of benefit may be lower because they are subject to a higher risk of death from competing causes and they are more medically fragile.

The sample did not include patients diagnosed with non-metastatic tumors whose tumors metastasized and were subsequently treated with chemotherapeutic agents. Thus, it is not representative of the population of patients treated with newer chemotherapeutic agents. We suspect that these patients have a better prognosis compared with patients initially diagnosed with metastatic disease.

We were unable to measure changes in patients' quality of life; it has probably improved over time. Although the effect of the newer chemotherapeutic agents on the occurrence of chemotherapeutic agent-induced adverse effects varies,²⁶⁻²⁸ newer agents delay tumor progression and increase the proportion of remaining survival time spent in a progression-free state.²⁸⁻³¹ Patients have also benefited from new antiemetic medications.

In keeping with established practice in cost analyses, we counted the portion of Medicare reimbursements for chemotherapeutic agents that exceeds manufacturers' expenses (ie, profit) as a cost. However, profits are not a true cost in the economic sense of the term.³²

New chemotherapeutic agents for colorectal cancer have been singled out as examples of high-cost/low-value medical care; no doubt they are the types of therapies that would receive close scrutiny if Medicare and other payers were to consider cost-effectiveness in coverage decisions. Our estimate of the cost per QALY gained, \$100 000, is below most estimates of the willingness to pay for a life-year.^{33,34} However, continuation of Medicare's open-ended coverage policy for new chemotherapeutic agents and other expensive technologies will prove difficult to sustain as costs for the program continue to rise.

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Author Contributions: Drs Howard, Kauh, and Lipscomb had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Howard and Kauh. *Acquisition of data:* Howard and Kauh. *Analysis and interpretation of data:* Howard, Kauh, and Lipscomb. *Drafting of the manuscript:* Howard and Kauh. *Critical revision of the manuscript for important intellectual content:* Howard, Kauh, and Lipscomb. *Statistical analysis:* Howard, Kauh, and Lipscomb. *Obtained funding:* Howard and Kauh. *Administrative, technical, and material support:* Kauh. *Study supervision:* Howard and Kauh. **Financial Disclosures:** None reported.

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